# Peptides at Membrane Surfaces and Their Role in Prebiotic Evolution

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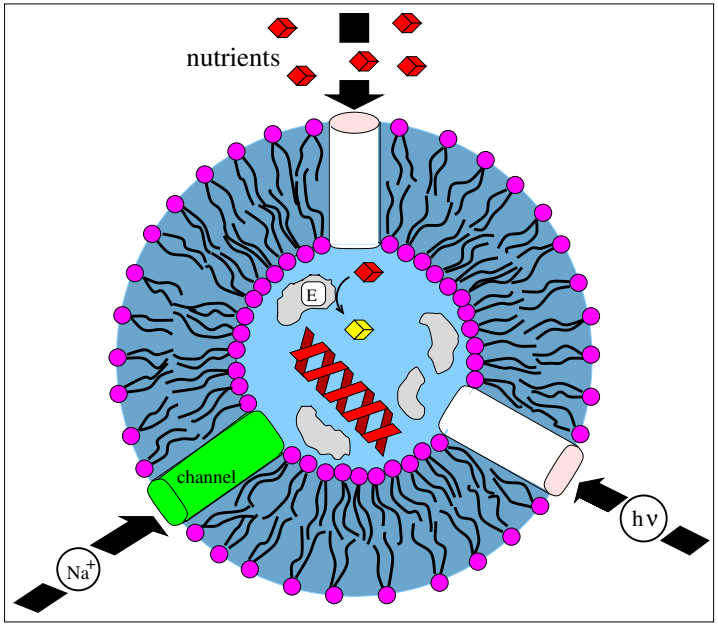
# Introduction

- What are necessary functions that protocells needed to perform?




- Membrane boundary separates inside from outside.
- Transport of ions, metabolites and waste (osmotic stress).
- Energy transduction.
- Peptides as precursors to modern proteins (**parsimony**).

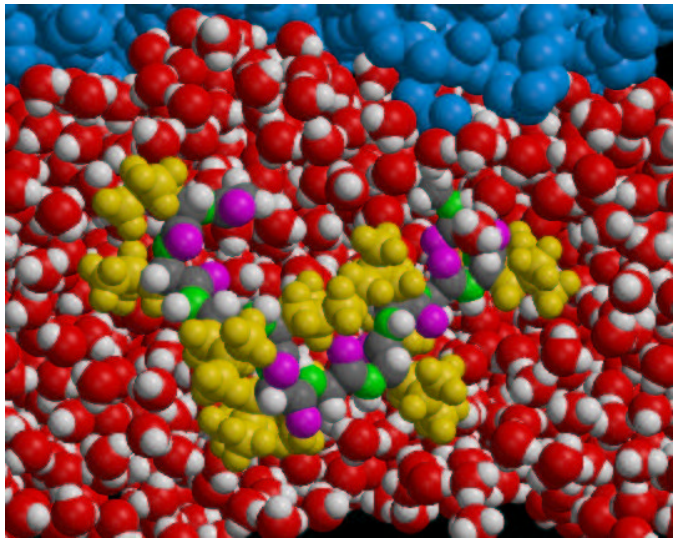
- Properties of the water/membrane interface promote **folding** and **association** of short peptides into units that could be **functional** enzymes and transporters.

- How? Investigate properties of water/membrane/peptide systems in Molecular Dynamics computer simulations.

# Membrane Assisted Folding

(Chipot and Pohorille, JACS, 1998)

- Undecamer of poly-L-leucine inserted into aqueous phase and equilibrated near the membrane.

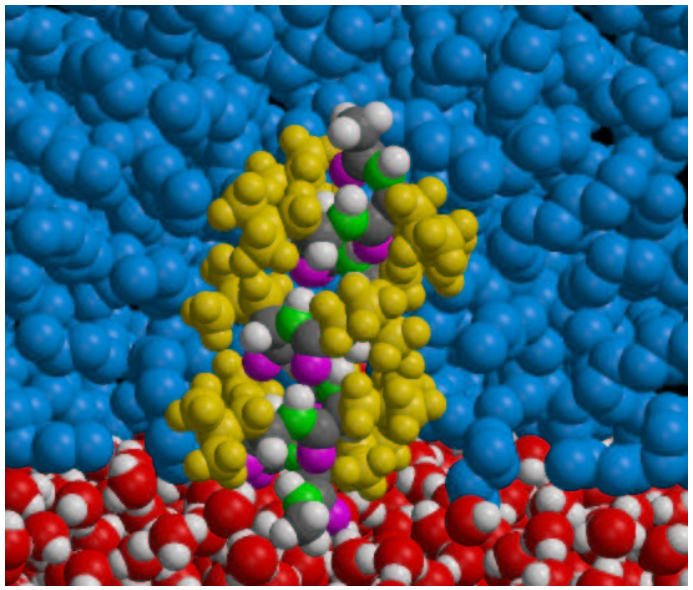


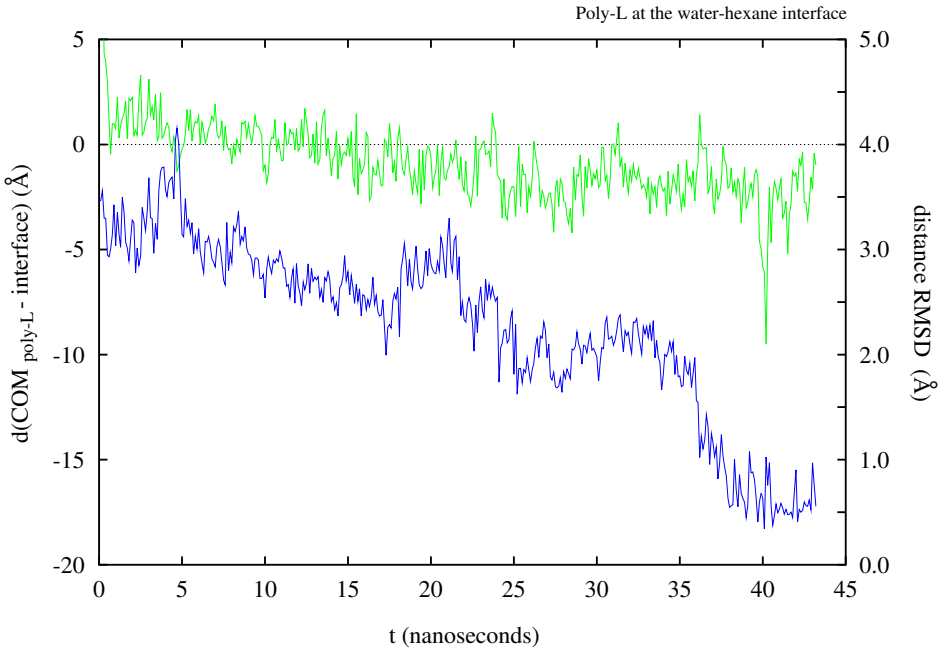
- In aqueous phase, the peptide exists as a random coil: water competes with backbone for H-bonding.
- This is a problem if small water-soluble peptides are to fold into well defined structures.

- How does the membrane affect the structure of the peptide?

# Poly-L in the Membrane

- The peptide simultaneously folds and inserts into the membrane.

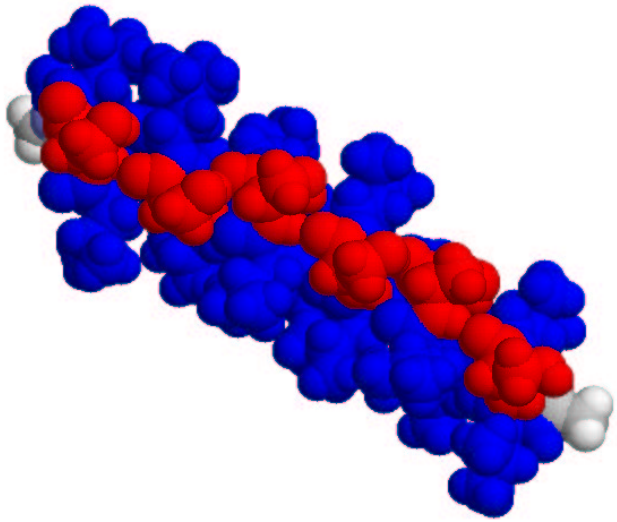





- Very fast: 10's of ns.
- Villin head piece domain (36 residues) is one of smallest folded water-soluble proteins (folds in microseconds).
- Perhaps a best case scenario: folded poly-L is hydrophobic. Mixed LQ peptides only partially folded.

# LS Peptide Description

- The $(LSLLLSL)_3$ peptide is a synthetic peptide which can form tetrameric, proton selective channels. (Lear, *et al.*, Science, 1988).

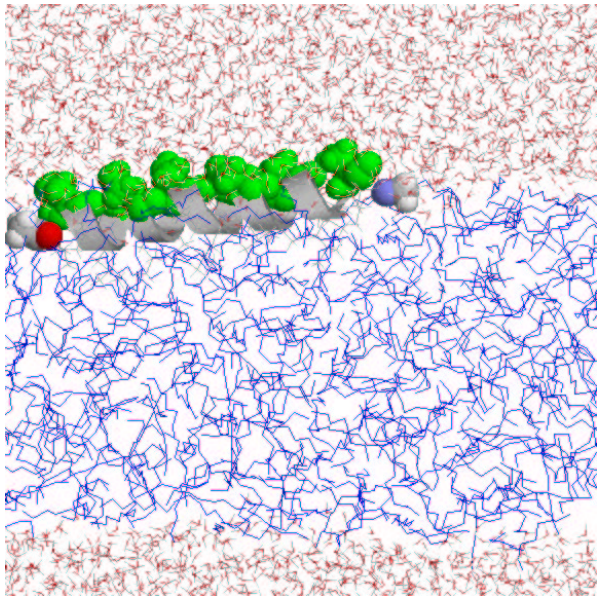


  - The $\alpha$-helical peptide has a hydrophilic and hydrophobic face: The amphipathic helix is surface active.
  - The "resting state" of the channel is likely helical monomers (and possibly dimers) oriented parallel to the interface.
  - Activation requires an electric field to orient the peptides perpendicular to the membrane. The channels persist for 1 ms. after the field is turned off.

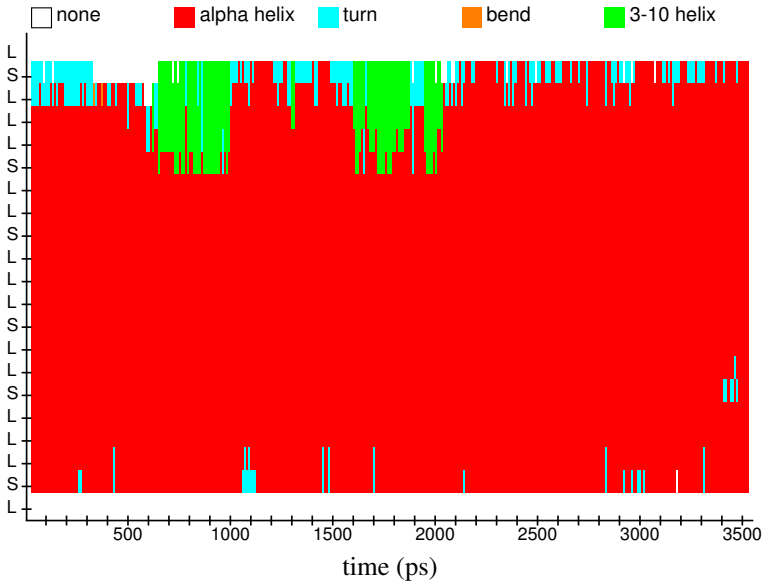
- Recent MD on $(LSLLLSL)_3$ bundles in a water-octane lamella (Zhong, *et al.*, Biophys. J., 1998) and in a POPC membrane (Randa, *et al.*, Biophys. J., 1999) have shown structures in good agreement with experiments.

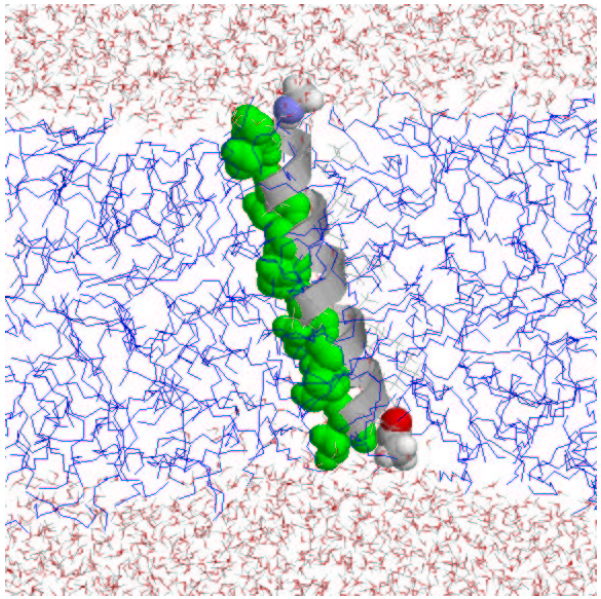
# Stability of LS Monomer

- Are the transmembrane and parallel surface-adsorbed states stable?

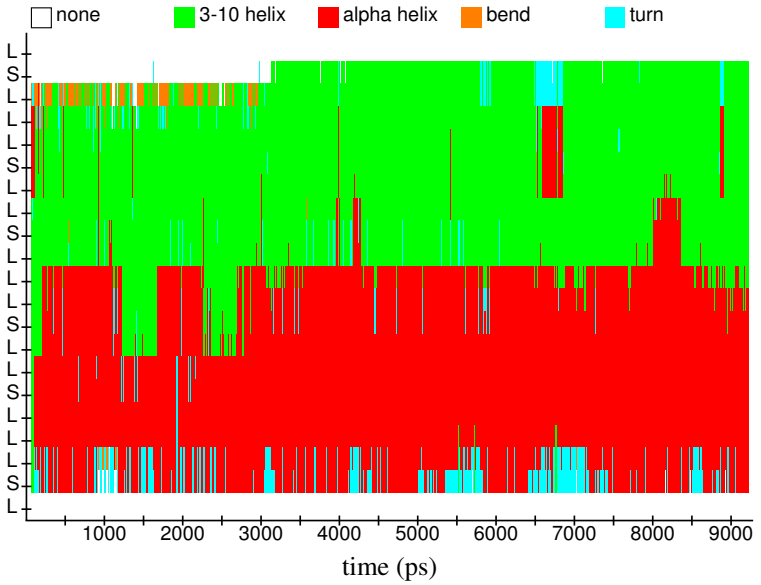


LS-Peptide parallel to interface



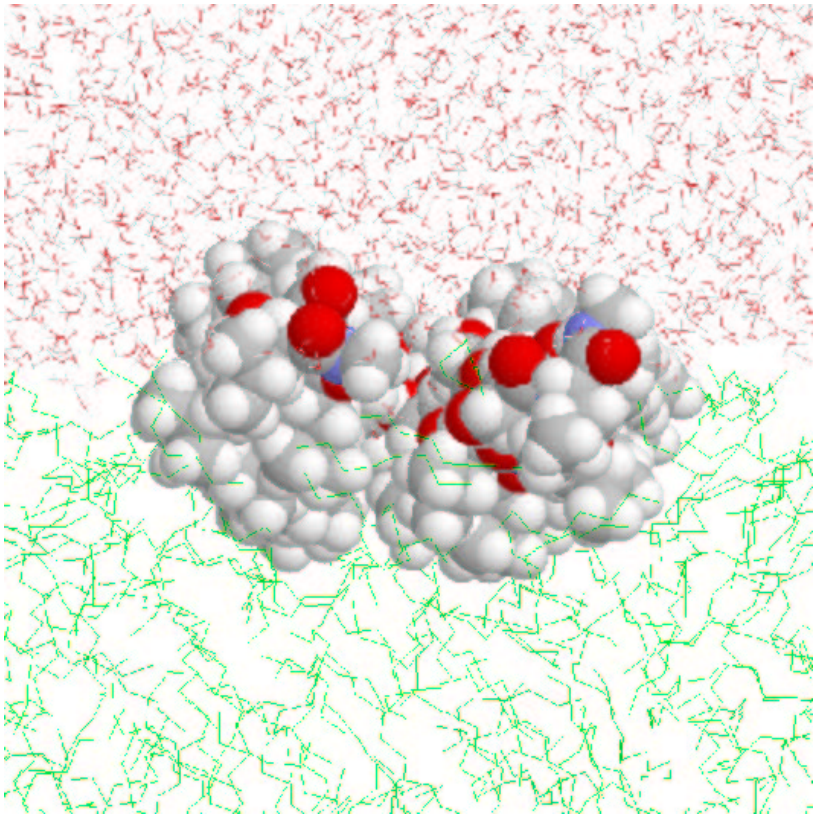



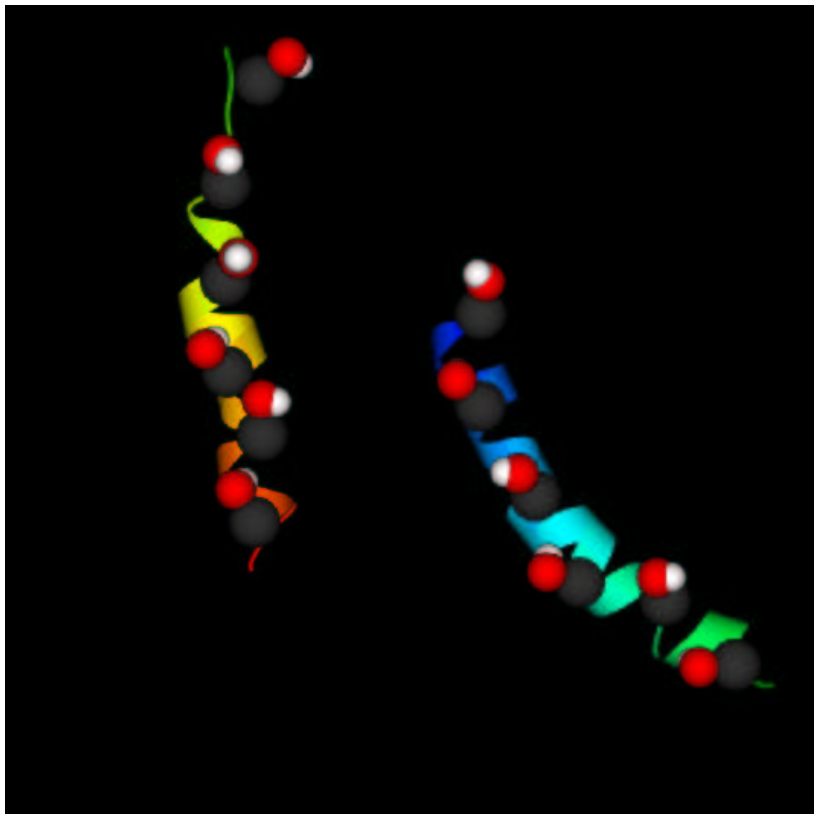
LS-Peptide normal to interface



# Stability of LS Dimers: In-plane orientation

- Dimer placed parallel to the water/membrane interface dissociates ($< 2$ ns.)

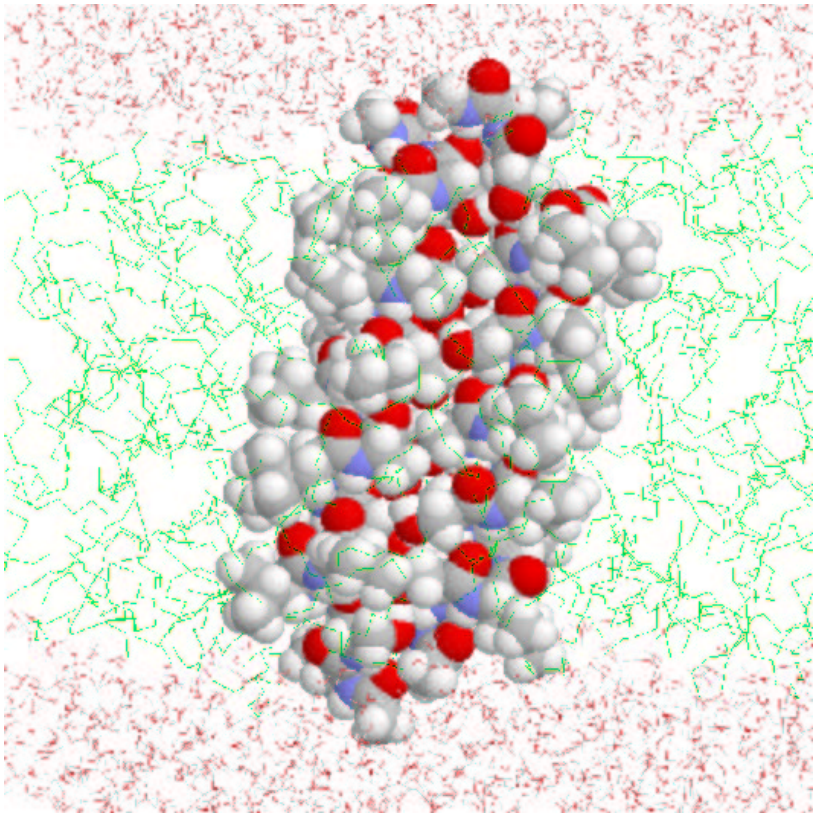


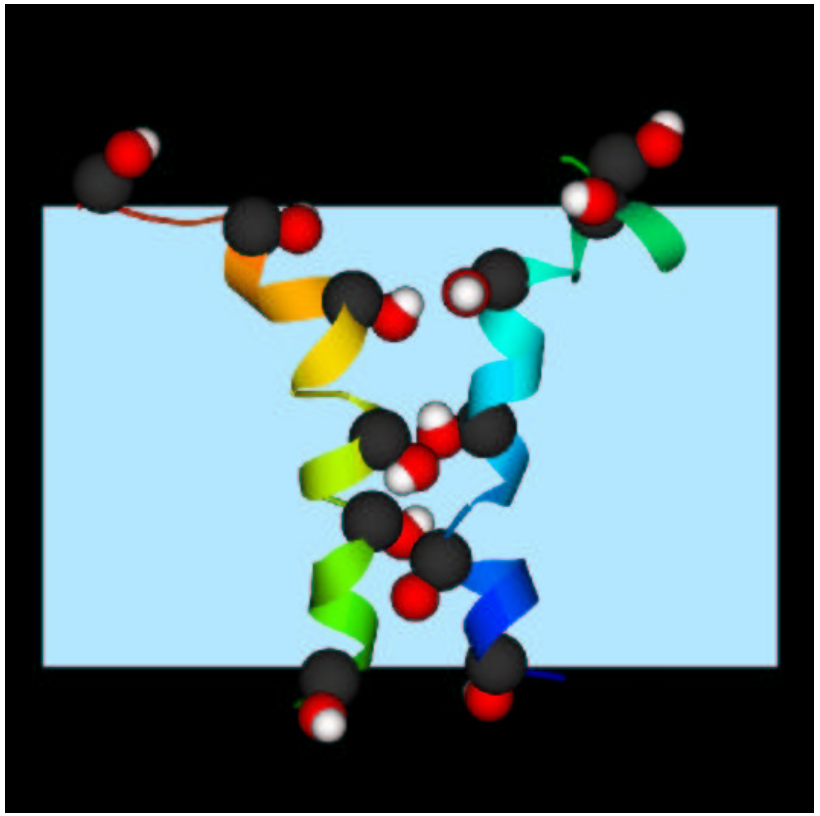


- Water-Ser for H-bonding wins out over Ser-Ser H-bonding.

# Stability of LS Dimers: Transmembrane

- Transmembrane dimer is stable on timescale of simulations ( $>$ 10 ns.)



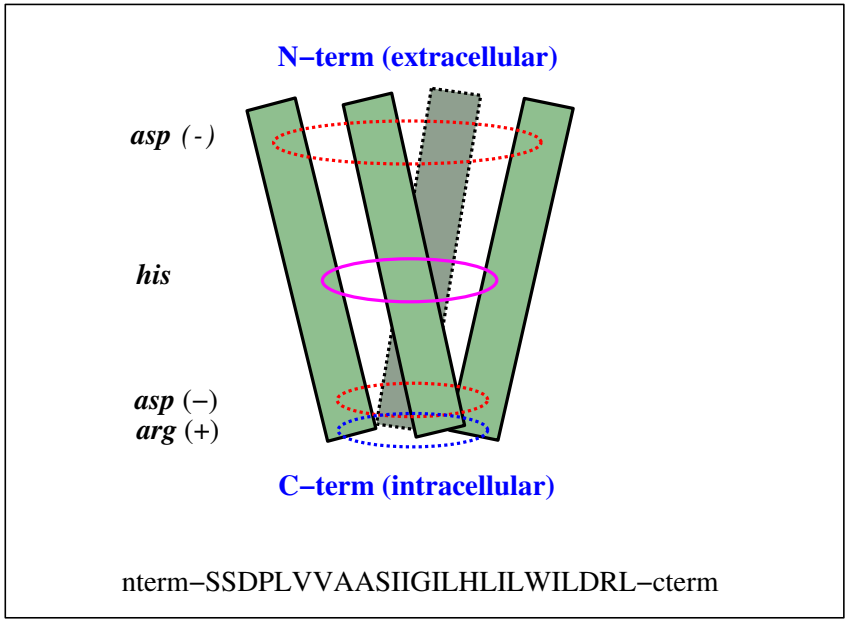


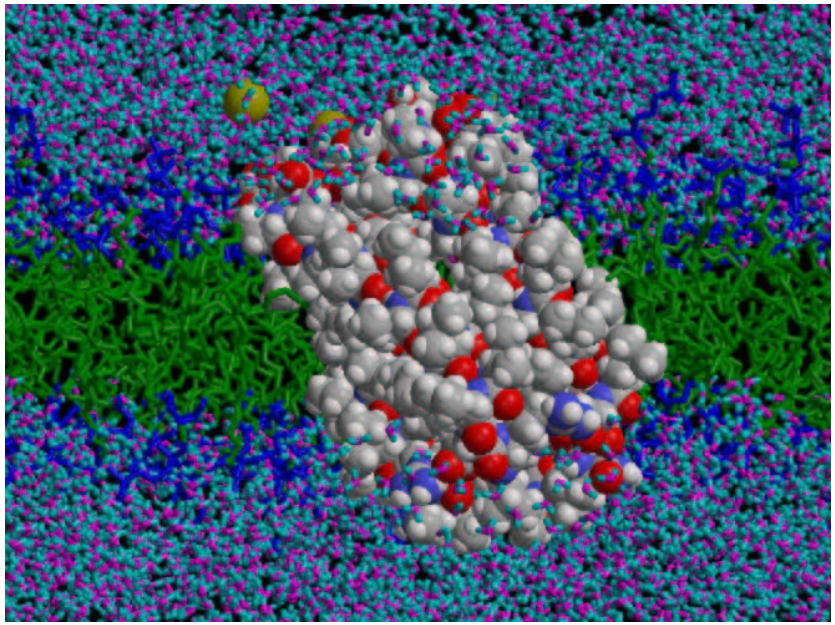
- Helices are loosely associated, with significant water penetration into the membrane interior.

# $M_2$ Transmembrane Fragment

(Schweighofer and Pohorille, Biophys J, 2000)

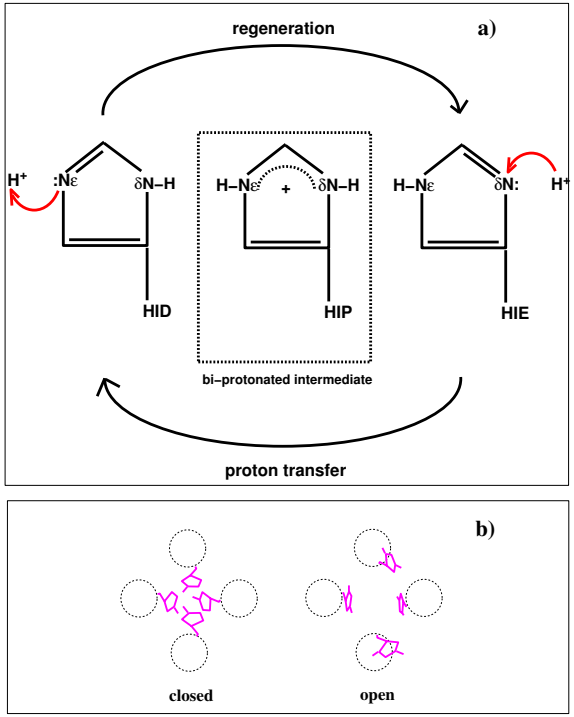
- Proton transport is central to bioenergetics in modern cells.
- The 25-residue transmembrane fragment of the Influenza A $M_2$ protein forms a proton channel. NMR and CD studies indicate it is a tetrameric bundle of $\alpha$-helices.

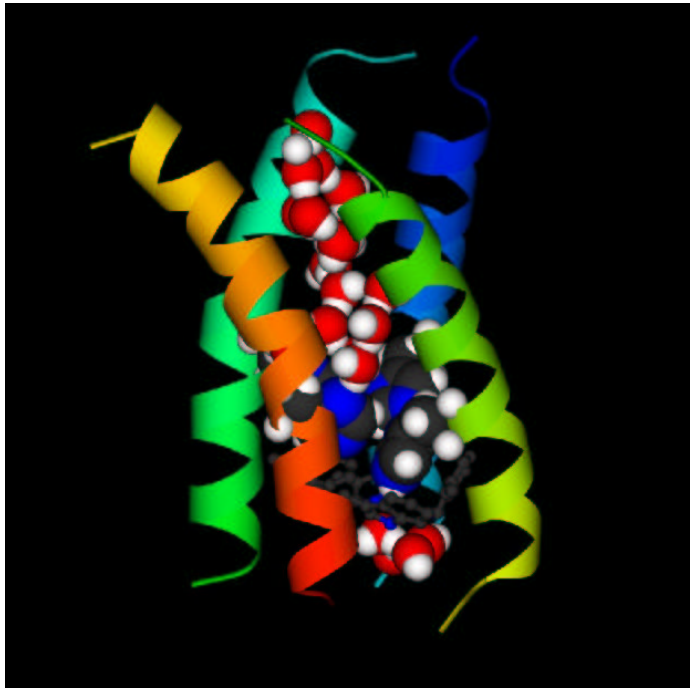


- The HIS (and possibly TRP) residues are thought to form a pH dependent "gate" to proton transport. What is the gating mechanism?

# Proton Transport in M2



- Multiply protonated HIS residues lead to unstable channels.
- Full water wires are not observed, which favors the shuttle mechanism.
- Need longer simulations of singly and doubly protonated channels.

# Conclusions

- Spontaneous **FOLDING** and **INSERTION** of short peptides occurs at water membrane surfaces. This is necessary for them to **FUNCTION** as channels.

- Transmembrane **ASSOCIATIONS** of simple peptides can function as channels. The Influenza $M_2$ channel provides a simple model for a pH gated proton selective channel: We want to understand the mechanism of proton transport and, more generally, how selectivity is achieved.

- We need to understand how to engineer simple, but specific, channels if we are to build laboratory models of "protocells."